



THE ROCKEFELLER UNIVERSITY

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JOSHUA LEDERBERG

July 28, 1986

PRESIDENT

Mr. E. Magruder Passano, Jr.
President
The Passano Foundation
428 East Preston Street
Baltimore, MD 21202

Dear Mr. Passano:

At your invitation, I am writing to nominate Dr. Attallah Kappas for the 1987 Passano Foundation Award.

Dr. Kappas is physician-in-chief of The Rockefeller University Hospital. He also heads the University's laboratory of metabolism-pharmacology, where he has devoted the past several years to basic and clinical research focused on heme, a compound involved in many important cellular processes and clinical problems. Heme binds with a protein, for example, to form hemoglobin, which transports oxygen in the blood. Heme also combines with certain other proteins to form cytochromes, enzymes that play an important role in the transformation of various chemicals and in energy transfer in the body.

Applying what he has learned about how heme is synthesized and degraded in the liver, Dr. Kappas has begun to construct chemical analogues of heme, which is a four-ring molecule with an iron atom at its center. By substituting other metals for the iron atom, Dr. Kappas has already produced two new hemes with unusual biological properties--work that has important clinical implications.

One of these synthetic hemes--tin-heme, which has a tin atom at its center--has shown great promise in preventing the excessive accumulation of bilirubin, a toxic chemical produced when the liver breaks down heme. In healthy adults, the liver excretes this toxin in bile. The immature liver of a newborn infant, however, is unable to process and excrete bilirubin produced during the first two weeks of life. In some newborns, accumulations of bilirubin cause severe jaundice; the toxin may also enter an infant's central nervous system, causing brain damage or death. Jaundice and other problems caused by excessive bilirubin also occur in adults whose livers are damaged by cirrhosis, hepatitis, and other liver diseases.

By administering tin-heme, Dr. Kappas inhibited the production of bilirubin, first in laboratory animals and, more recently, in

humans. At present, clinical trials are proving successful at the largest hospital in Singapore, where it is being administered to newborns with jaundice, and at the prestigious Karolinska Institute in Sweden, where it is being used to treat patients with a liver disease that primarily afflicts middle-aged women.

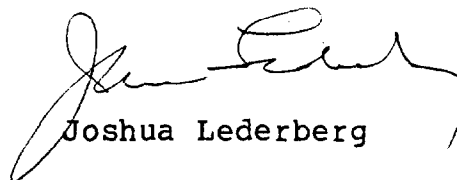
Tin-heme prevents the production of the toxin by blocking the access of natural heme to the enzyme that catalyzes the formation of bilirubin. Unable to bind to this enzyme, natural heme--with the iron atom at its center--is released from the body unaltered. This effect of administering tin-heme--the removal of iron from the body--may also have considerable clinical significance, because excess iron is responsible for many of the pathological effects of certain liver diseases, sickle cell anemia, a genetic disease known as thalassemia, and several other disorders.

In related research focused on the heme-containing compound cytochrome P450, Dr. Kappas has made major contributions to the scientific understanding of how specific alterations in diet affect the way in which the human body metabolizes medicinal drugs, environmental chemicals, steroid hormones, and other substances produced by the body. Dr. Kappas has discovered, for example, that cruciferous vegetables, such as cabbages and Brussels sprouts, dramatically accelerate drug metabolism; charcoal-broiled steak can speed it almost tenfold.

The already demonstrated clinical importance of Dr. Kappas's research and the wide range of its potential practical applications make him an excellent candidate for a Passano Award. Although these achievements have not yet attracted wide public attention, I hope the directors of the Passano Foundation and their medical advisers will give Dr. Kappas their most serious consideration.

Thank you.

Sincerely,



Joshua Lederberg

JL:pf

Enclosure